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石杉碱甲治疗老年期记忆障碍的药物评价

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Drug evaluation of huperzine A in the treatment of senile memory disorders

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ABSTRACT Huperzine A is an alkoloid which was first isolated from *Huperzia serrata* (Thumb) Trev by Zhejiang Academy of Medical Sciences and Shanghai Institute of Materia Medica, Chinese Academy of Sciences. It exhibits a significant anticholinesterase activity and has been used on myasthenia gravis patients. The therapeutic effects were studied by random, match and double-blind method on 56 patients of multi-infarct dementia or senile dementia and 104 patients of senile and presenile simple memory disorders. The curative effects were evaluated by Wechsler memory scale. The im dose for multi-infarct dementia was 0.05 mg bid for 4 wk, whereas that for senile and presenile simple memory disorders was 0.03 mg bid for 2 wk. Saline was used on control group. The result showed that the curative effect of huperzine A was significant. Only a few patients felt slight dizziness and this did not affect the therapeutic effects.

KEY WORDS huperzine A; memory disorders; senile dementia; multi-infarct dementia; drug evaluation

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提要 本文观察了石杉碱甲对多发梗死性痴呆或合并老年性痴呆病人 56 例，老年及初老期单纯记忆障碍患者 104 例的治疗作用. 采用随机分组、配对及双盲法试验，以韦氏记忆量表评定疗效. 剂量分别为 50 μg 和 30 μg、im、bid. 疗程分别为 4 wk 和 2 wk. 对照用生理盐水. 结果证实石杉碱甲疗效显著，极个别病人有轻度、短暂的头昏反应.

关键词 石杉碱甲；记忆障碍；老年性痴呆；多发梗死性痴呆；药物评价

石杉碱甲(huperzine A，Hup-A)是浙江省医学科学院和中国科学院上海药物研究所从石杉科石杉属植物 *huperzia serrata* (Thunb) Trev (蛇足石杉)中提取的治疗重症肌无力新药，系可逆性乙酰胆碱酯酶(AChE)抑制剂，抑制强度是毒扁豆碱(Phys)的 3 倍[1]. Phys 通过拟胆碱机制能改善学习与记忆功能，但因副作用大、$T_{\frac{1}{2}}$短而难以临床应用[2,3]. 为开拓 Hup-A 在该领域的适应症，我们以老年痴呆和单纯记忆障碍为研究对象，采用配对、双盲试验，以韦氏记忆量表(Wechsler memory scale，WMS)评定疗效. 结果证实 Hup-A 具有确切临床适用价值，现报道如下.

MATERIALS AND METHODS

病例来源与选择 痴呆患者 56 人来自本课题协作组的 4 个医院，男 52 人，女 4 人. 单纯记忆障碍患者 104 人来自协作组另 4 个医院，男 58 人，女 46 人. 痴呆组：年龄 64±SD 7 yr，或虽 <60 yr，但有卒中史并已稳定 2 yr 以上；WMS 测定记忆商(memory quotient，MQ) <90，>50；颅脑 CT 片示有梗塞灶或/和脑萎缩；无严重视、听、触觉或运动障碍. 以痴呆诊断标准[4]为依据，结合常规

心、肝、肾、内分泌以及 EEG、CT 等检查，由两名神经科医师签名确立诊断. 单纯记忆障碍组:年龄 > 45 yr，主诉记忆力明显下降；WMS 测定 MQ < 100，> 50，无视、听、触觉或运动障碍；结合常规心、肝、肾、内分泌、EEG、CT 等检查排除各种器质性、代谢性、中毒性脑病，神经系统检查阴性.

配对与双盲试验 痴呆病人全部住院，单纯记忆障碍患者在不影响设计要求的前提下，可以门诊观察. 全部受试对象按性别、文化程度，年龄差 ± 5 yr 及 MQ ± 10 分进行配对，随机分为治疗组和对照组. 两组用药由浙江省医学科学院药物研究所统一制备，其包装、外形、颜色和 pH 一致，使受试者和临床医师均无法区别.

剂量、疗程与疗效考核 治疗用药均为 im 1 ml，痴呆组含 Hup-A 50 μg，单纯记忆障碍组含 Hup-A 30 μg，空白对照用盐水，均为 bid，痴呆组 4 wk 为一疗程，单纯记忆障碍组 2 wk 为一疗程，自受试前 1 wk 停用促智药、拟胆碱或抗胆碱药、中枢兴奋剂或抑制剂，降压药、酒类以及中成药类滋补剂等，以排除其他药物干扰. 以湖南医学院修订的 WMS 测定为客观依据. 治疗前后分别采用 WMS 甲式和乙式测定，两次检查间隔期不得少于 5 wk，疗程结束的检查需在 im 药物后 1-3 h 内进行.

显著性测验 按 t test 的配对及组间比较法.

RESULTS

痴呆治疗效果 Tab 1，治疗组($n = 28$)治疗前后 WMS 检查结果之 MQ 值，差异显著($P < 0.01$). 而对照组治疗前后 WMS 检查结果之 MQ 值，相差不显著($P > 0.05$).

单纯记忆障碍治疗效果 Tab 1，治疗组($n = 52$)治疗前后 WMS 检查结果之 MQ 值，相差显著($P < 0.01$)而对照组治疗前后 WMS 检查结果之 MQ 值，无显著差异($P > 0.05$).

治疗组和对照组比较 Tab 1 显示两病种治疗组与对照组间的性别、年龄、MQ 值均无统计学差异. 经一个疗程治疗后，痴呆及单纯记忆障碍患者的治疗组与对照组之间 MQ 值比较，都有显著差异($P < 0.01$).

Tab 1. Match analysis of im huperzine A in treatment of 56 patients of multi-infarct dementia or senile demeotia and 104 patients of simple memory disorders. MQ = memory quotient. $\bar{x} \pm SD$, $^{*}P > 0.05$, $^{***}P > 0.01$ *vs* control; $^{+}P > 0.05$, $^{+++}P < 0.01$ *vs* before treatment.

	Control group	Treated group
Dementia	28	28
Male	26	26
Female	2	2
Age	64 ± 6	64 ± 7*
Dosage	1 ml NS bid	Hup A 50 μg bid
Course of treatment	4 wk	4 wk
MQ before treatment	73 ± 12	73 ± 12*
MQ after treatment	77 ± 13+	88 ± 17***+++
Simple memory disorder	52	52
Male	29	29
Female	23	23
Age	62 ± 6	63 ± 7*
Dosage	1 ml NS bid	Hup A 30 μg bid
Course of treatment	2 wk	2 wk
MQ before treatment	76 ± 12	74 ± 13*
MQ after treatment	79 ± 14+	90 ± 15***+++

不良反应 在治疗过程中未发现明显毒副反应. 仅个别病人有轻度头昏，持续时间短暂，不需特殊处理.

DISCUSSION

随着人群年龄结构的老化，老年记忆障碍或痴呆病已成为急待解决的临床问题. 本研究经临床验证，WMS 检查表明痴呆治疗组经 Hup-A 治疗前后 MQ 值以及与对照组治疗后

的 MQ 值比较，都有显著差异($P<0.01$). 单纯记忆障碍治疗组治后 MQ 值与治前 MQ 值以及与对照组治疗后的 MQ 值比较也有显著差异($P<0.01$). 本文结果与唐氏、陆氏的动物迷宫试验结论[5,6]完全一致.

学习、记忆障碍的机理与中枢胆碱能系统的密切关系已被国内外学者所公认[1,2]. 继 Phys 之后，近期报道的有槟榔碱、毛果芸香碱和人工合成的四氢氨基吖啶(THA)[7]. 但因毒性大，作用时间短或疗效不太确切而未能满意地应用于临床. 唯一获得美国 FDA 批准的氢化麦角碱(Hydergine)，也有直立性低血压和价格昂贵的缺点. Hup-A 作为新型胆碱酯酶抑制剂. 自 1985 年问世以来，不仅有广泛的临床适应症，而且该药的突出优点还在于药效持续时间较长[8]. 治疗记忆障碍的剂量仅为重症肌无力治疗剂量的 1/10，剂量与效应关系有明显易化现象，具有较大治疗指数[5,9]. 本品口服吸收快，生物利用度高达 96.9%[10]. 若改用口服给药可望发展成为一种使用方便、有效的增强记忆和改善老年性痴呆症状的新制剂.

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